General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium guidelines for *CYP2C19* genotype and clopidogrel therapy: 2013 update.

Bibliographic Source(s)

Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013 Sep;94(3):317-23. [40 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Scott SA, Sangkuhl K, Gardner EE, Stein CM, Hulot JS, Johnson JA, Roden DM, Klein TE, Shuldiner AR; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin Pharmacol Ther. 2011 Aug;90:328–32.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Genetic Test Interpretation

Clinical genotyping tests are available that interrogate variant *cytochrome P450 (CYP)2C19* alleles and predict an individual's *CYP2C19* metabolizer phenotype. Each named star (*) allele is defined by the genotype at one or more specific single-nucleotide polymorphisms (see Supplementary Table S1 online [see the "Availability of Companion Documents" field]) and is associated with a level of enzyme activity (see Supplementary Table S2 online [see the "Availability of Companion Documents" field]). Table 1 below and Supplementary Table S5 online (see the "Availability of Companion Documents" field) summarize the assignment of the likely *CYP2C19* phenotype based on common star allele diplotypes, and these assignments are used to link genotypes with personalized antiplatelet therapy.

Table 1. Assignment of Likely *CYP2C19* Phenotypes Based on Genotypes

Likely Phenotype	Genotypes	Examples of Diplotypes
Ultrarapid metabolizer: normal or increased	An individual carrying two increased activity alleles (*17) or one functional	*1/*17,

Likely Phenotype	Genotypes	Examples of Diplotypes
activity (~5–30% of patients)	allele (*1) plus one increased-activity allele (*17)	*17/*17
Extensive metabolizer: homozygous wild-type or normal activity (~35–50% of patients)	An individual carrying two functional (*1) alleles	*1/*1
Intermediate metabolizer: heterozygote or intermediate activity (~18–45% of patients)	An individual carrying one functional allele (*1) plus one loss-of-function allele (*2–*8) or one loss-of-function allele (*2–*8) plus one increased-activity allele (*17)	*1/*2, *1/*3, *2/*17
Poor metabolizer: homozygous variant, mutant, low, or deficient activity (~2–15% of patients)	An individual carrying two loss-of-function alleles (*2–*8)	*2/*2, *2/*3, *3/*3

Some rare genotype combinations have unclear predicted metabolic phenotypes; see Supplementary Table S5 online (see the "Availability of Companion Documents" field).

Therapeutic Recommendations

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are designed to help clinicians understand how available genetic test results can be used to optimize drug therapy rather than to recommend in whom pharmacogenetic testing should be conducted. With the growing ease and availability of genetic testing and other sequencing programs, an increasing number of patients in the near future may already know their *CYP2C19* genotype status at the time of treatment, and this document provides guidance on clinical management for those in whom genotype is available or for whom the clinician chooses to order a *CYP2C19* genotyping test. With respect to other professional statements, the 2012 American College of Cardiology Foundation/American Heart Association acute coronary syndrome (ACS) guidelines noted that genetic testing for *CYP2C19* loss-of-function alleles may be considered on a case-by-case basis, especially for patients who experience recurrent ACS events despite ongoing therapy with clopidogrel. In addition, the committee recommended that genotyping might be considered if results of testing may alter management, which they suggest until better clinical evidence exists to provide a more scientifically derived recommendation.

Optimal individualized antiplatelet treatment should maximize benefit by reducing risk of recurrent cardiovascular (CV) events while minimizing adverse effects such as bleeding. Prasugrel is an approved antiplatelet agent that was superior to clopidogrel in a large-scale randomized trial of ACS patients with planned percutaneous coronary intervention (PCI), with a hazards ratio (HR) for CV death, myocardial infarction, or stroke for prasugrel vs. clopidogrel of 0.81 (95% confidence interval [CI] = 0.73–0.90, P <0.001), as well as a 42% reduction in stent thrombosis. However, it may not represent a substitute for clopidogrel in all patients due to an increased risk of non-coronary artery bypass grafting thrombolysis in myocardial infarction (TIMI) major bleeding (HR = 1.32, 95% CI =1.03–1.68; P = 0.03), including fatal bleeding (prasugrel = 0.4% vs. clopidogrel = 0.1%; P = 0.002); its contraindication in some patients (e.g., history of transient ischemic attack, stroke, or intracranial bleeding); and the lower expense of generic clopidogrel following the recent expiration of its patent. Of note, the benefit of prasugrel over clopidogrel was found to be greater in patients with a *CYP2C19* loss-of-function allele, with no significant difference estimated in composite outcome risk between the two antiplatelet agents among *CYP2C19* extensive metabolizers (i.e., **1/*1* patients).

In addition to prasugrel, ticagrelor is a recently approved antiplatelet agent that also was superior to clopidogrel in a large-scale randomized trial of ACS patients with an HR for CV death, myocardial infarction, or stroke for ticagrelor vs. clopidogrel of 0.84 (95% CI = 0.77–0.92; P <0.001), including a 26% reduction in stent thrombosis and 18% reduction in all-cause mortality. In the genetic substudy, as compared with clopidogrel, ticagrelor reduced the primary end point by 23% among patients carrying any *CYP2C19* loss-of-function allele (8.6 vs. 11.2%; HR = 0.77, 95% CI = 0.60–0.99; P = 0.0380) and 14% among patients without any *CYP2C19* loss-of-function allele (8.8 vs. 10.0%; HR = 0.86, 95% CI = 0.74–1.01), although this reduction did not reach statistical significance (P = 0.0608). However, formal interaction testing that evaluated if the effect of ticagrelor vs. clopidogrel varied by genotype was also not significant. Of note, the benefit of ticagrelor as compared with clopidogrel was subsequently shown to appear to be most pronounced among the subset of patients with *CYP2C19* loss-of-function alleles who were undergoing PCI (carriers: 7.7 vs. 10.6%, HR = 0.71; noncarriers: 7.4 vs. 8.2%, HR = 0.90). In addition, it is not known to what extent twice-daily dosing may affect the efficacy of ticagrelor relative to clopidogrel in a real-world setting.

Despite the improvements in overall efficacy reported for prasugrel and ticagrelor as compared with clopidogrel, it is anticipated that clopidogrel will continue to be a widely prescribed medication for ACS/PCI patients. Genotype-directed therapy could identify patients who benefit most from alternative antiplatelet therapy. For clinicians considering treatment with clopidogrel, Table 2 below and Figure 1 in the original guideline document summarize the therapeutic recommendations for antiplatelet therapy based on *CYP2C19* status. Standard dosing of clopidogrel, as recommended in the product insert, is warranted among ACS/PCI patients with a predicted *CYP2C19* extensive metabolizer or ultrarapid metabolizer phenotype (i.e., **1/*1, *1/*17*, and **17/*17*). If genotyping from a Clinical Laboratory Improvement Amendments–certified laboratory identifies a patient as a *CYP2C19* poor metabolizer (PM) (i.e., **2/*2*), current literature supports the use of an alternative antiplatelet agent (e.g., prasugrel or ticagrelor) when not contraindicated clinically.

The most challenging patient population to address is the *CYP2C19* intermediate metabolizer (IM) phenotype (e.g., **1/*2, *1/*3*, and **2/*17*).

IMs have higher on-treatment residual platelet activity on average as compared with extensive metabolizers, and ACS/PCI *CYP2C19*2* heterozygotes treated with clopidogrel have increased risks for serious adverse CV outcomes, including stent thrombosis (see Supplementary Materials and Methods online [see the "Availability of Companion Documents" field]). Consequently, these data support switching to an alternative antiplatelet agent for IMs when not contraindicated. However, given the wide interindividual variability in residual platelet activity observed among clopidogrel-treated IMs, clinical judgment also taking into account other factors that may place an IM at increased risk of a CV event (or adverse bleeding event) must be considered to most effectively individualize therapy.

In addition, although these guidelines have been focused on *CYP2C19*2* and **3*, many clinical genotyping platforms include other variant alleles (e.g., **4–*8* and **17*) that can alter a patient's predicted metabolizer phenotype interpretation (see Supplementary Table S5 online [see the "Availability of Companion Documents" field]). As mentioned above, the **4–*8* alleles have strong *in vitro* evidence for complete loss of function of the *CYP2C19* enzyme. Consequently, when these alleles are identified among ACS/PCI patients treated with clopidogrel, they should be considered as influencing clopidogrel metabolism and clinical outcomes consistent with the **2* loss-of-function allele.

Table 2. Antiplatelet Therapy Recommendations Based on *CYP2C19* Status When Considering Clopidogrel for ACS/PCI Patients

Phenotype (Genotype)	**Implications for Clopidogrel**	**Therapeutic Recommendations**	**Classification of Recommendations**
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation[a]	Clopidogrel: label-recommended dosage and administration	**Strong**
Intermediate metabolizer (*1/*2, *1/*3, *2/*17)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	**Moderate**
Poor metabolizer (*2/*2, *2/*3, *3/*3)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	**Strong**

[a]The *CYP2C19*17* allele may be associated with increased bleeding risks.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

An algorithm titled "Algorithm for suggested clinical actions based on CYP2C19 genotype when considering treatment with clopidogrel for ACS patients undergoing PCI (ACS/PCI)" is provided in the original guideline document.

Scope

Disease/Condition(s)

Diseases and conditions requiring antiplatelet therapy, particularly among patients with acute coronary syndromes undergoing percutaneous coronary intervention

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Cardiology

Family Practice

Internal Medicine

Medical Genetics

Pharmacology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To update the 2011 Clinical Pharmacogenetics Implementation Consortium guideline on the clinical use of *cytochrome P450 (CYP)2C19* genotype test results for patients requiring antiplatelet therapy
- To help clinicians understand how available *CYP2C19* genetic test results can be used to optimize clopidogrel drug therapy

Target Population

Patients requiring antiplatelet therapy, particularly patients with acute coronary syndromes undergoing percutaneous coronary intervention

Interventions and Practices Considered

Use of antiplatelet therapy (clopidogrel, prasugrel, ticagrelor) based on *cytochrome P450* (*CYP*)*2C19* genotype

Major Outcomes Considered

- Risk for serious adverse cardiovascular events, such as cardiovascular death, myocardial infarction, stroke, or stent thrombosis in relation to *cytochrome P450 (CYP)2C19* genotypes
- Adverse effects of antiplatelet agents in relation to *CYP2C19* genotypes

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The PubMed database (National Center for Biotechnology Information [NCBI]) was searched using the keywords (CYP2C19 OR cytochrome P450-2C19) AND (clopidogrel) from 1966 to January 2013.

To construct a *cytochrome P450 (CYP)2C19* minor allele frequency table based on ethnicity, the PubMed database (1966 to January 2011) and Ovid MEDLINE (1950 to January 2011) were searched using the following criteria: ((CYP2C19 or 2C19) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity)) with filter limits set to retrieve "full-text" and "English" literature. Studies were considered for inclusion if: (1) the ethnicity of the population was clearly indicated; (2) either allele frequencies or alleles for *CYP2C19* genotypes were reported; (3) the method by which *CYP2C19* was genotyped appeared reliable; (4) the sample population consisted of at least 50 individuals; and (5) the study represented publication of novel data (no reviews or meta-analyses). In instances where genotype data from large cohorts of ethnically-diverse individuals were reported, without respect to ethnicity, studies were only considered if one ethnicity was ≥95% of the majority.

The combined analysis grouped subpopulations based on the Human Genome Diversity Project-Centre Etude Polymorphism Humain (HGDP-CEPH) and included 7,970 Africans, 7,920 Americans, 36,030 East Asians, 121,808 Europeans, 2,140 Middle Easterns, 13,742 Oceanians, and 7,248 South/Central Asians.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence Linking Genotype to Phenotype

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Clinical Pharmacogenetics Implementation Consortium (CPIC) therapeutic recommendations are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* clinical outcome data for clopidogrel, *in*

vivo pharmacokinetic and pharmacodynamic data for clopidogrel, *in vitro* enzyme activity of expressed wild-type or variant-containing *cytochrome P450 (CYP)2C19*, *in vitro CYP2C19* enzyme activity from tissues isolated from individuals of known *CYP2C19* genotypes, *in vivo* pre-clinical pharmacokinetic and pharmacodynamic studies, and *in vitro* studies of *CYP2C19* protein stability or enzyme activity.

Based on previously published criteria, a simple scale of high, moderate or weak to grade the levels of evidence has been implemented (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. The Clinical Pharmacogenetics Implementation Consortium uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf) (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Every effort was made to present evidence from high-quality studies and to take into consideration all available peer-reviewed published literature, which provided the framework for the strength of therapeutic recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Optimal individualized antiplatelet treatment should maximize benefit by reducing risk of recurrent cardiovascular (CV) events while minimizing adverse effects such as bleeding.
- Genotype-directed therapy could identify patients who benefit most from alternative antiplatelet therapy.
- The potential benefits of *cytochrome P450 (CYP)2C19* testing are that when considering treatment with clopidogrel in acute coronary syndrome (ACS)/percutaneous coronary intervention (PCI) patients, genotypes that confer a higher risk of a CV event on clopidogrel can be identified, and an alternative antiplatelet strategy can be instituted.

Potential Harms

- *Cytochrome P450 (CYP)2C19* loss-of-function alleles confer increased risks for serious adverse cardiovascular (CV) events among clopidogrel-treated patients with acute coronary syndromes (ACSs) undergoing percutaneous coronary intervention (PCI).
- Some studies indicate that the common *CYP2C19*17* allele results in enhanced platelet inhibition and clopidogrel response and perhaps an increased risk of bleeding complications.
- Large meta-analyses have shown that clopidogrel-treated ACS patients undergoing PCI who are *CYP2C19*2* heterozygotes or homozygotes have an increased risk for major adverse CV events as compared with **1* homozygotes (hazard ratio [HR] = 1.55, 95% confidence interval [CI] = 1.11–2.17 for heterozygotes; HR = 1.76, 95% CI = 1.24–2.50 for homozygotes) and increased risks of stent thrombosis (HR = 2.67, 95% CI = 1.69–4.22 for heterozygotes; HR = 3.97, 95% CI = 1.75–9.02 for homozygotes).
- A lack of effect of *CYP2C19* loss-of-function alleles on adverse CV outcomes has been reported among clopidogrel-treated patients with lower clinical risks and/or other indications (e.g., atrial fibrillation, stroke).
- Although *CYP2C19* genotyping is straightforward and reliable when performed in qualified laboratories, as with any laboratory test, an additional possible risk to the patient is an error in genotyping. Because genotypes are lifelong test results, any such error could have adverse health implications for the life of the patient.

See "Implications for Clopidogrel" in Table 2 of the original guideline document for more information.

Contraindications

Contraindications

Prasugrel is contraindicated in some patients (e.g., history of transient ischemic attack, stroke, or intracranial bleeding).

Qualifying Statements

Qualifying Statements

Although there is mounting evidence associating deficient *cytochrome P450 (CYP)2C19* with increased risks of adverse cardiovascular outcomes in clopidogrel-treated acute coronary syndrome (ACS)/percutaneous coronary intervention (PCI) patients, the absence of randomized clinical trial evidence that *CYP2C19* genotyping improves outcomes must be acknowledged.

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

If pursuing *CYP2C19* genotyping, one of the challenges is the need for rapid turnaround time of results. It would be advantageous to have the results before initiating antiplatelet therapy because the majority of potentially preventable recurrent events occur early in treatment. For example, among other clinical and genetic factors, *CYP2C19*2* has recently been associated with definite early stent thrombosis in a case–control study. Therefore, if *CYP2C19* genotype is not already known from prior testing, early testing and expedited reporting would be advantageous. To address this issue, point-of-care genetic testing systems have been developed (see Supplementary Materials and Methods online; see the

"Availability of Companion Documents" field), and some academic medical centers have deployed preemptive genotyping programs for selected patient populations.

Of note, as described above, these recommendations apply predominantly to ACS patients undergoing PCI. Current data do not support the use of *CYP2C19* genotype data to guide treatment in other scenarios. In addition, at the time of this writing, there are no data available on the possible role of *CYP2C19* in clopidogrel response in pediatric patient populations; however, there is no reason to suspect that *CYP2C19* variant alleles would affect clopidogrel metabolism differently in children as compared with adults.

Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to persons or property arising out of or related to any use of CPIC's guidelines, or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013 Sep;94(3):317-23. [40 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Aug (revised 2013 Sep)

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

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Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

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Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Scott SA, Sangkuhl K, Gardner EE, Stein CM, Hulot JS, Johnson JA, Roden DM, Klein TE, Shuldiner AR; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin Pharmacol Ther. 2011 Aug;90:328–32.

Guideline Availability

Electronic copies: Available from Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

The following are available:

- Supplementary material, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site .
- An interactive dosing table is available at the Pharmacogenomics Knowledgebase Web site .
- A clopidogrel metabolism pathway is also available from the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 31, 2013. The information was verified by the guideline developer on December 6, 2013.

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